pending claims 28-38). Claims 1-17 and 24-27 are cancelled without prejudice as drawn to a non-elected invention.

Information Disclosure Statement

Applicants concur that on January 19, 1999 an IDS was submitted to the Patent and Trademark Office for this case. On November 29, 1999 Applicants submitted an IDS to the Patent and Trademark Office that included these references. Submitted herewith is a copy of the IDS as filed on January 19, 1999 as well as a copy of the Express Mail receipt demonstrating that the IDS originally was submitted on January 19, 1999 (Exhibit A).

Oath/Declaration

Applicants concur that the correct zip code for Dr. Walt is 02421 as noted by the Examiner. Applicants appreciate the Examiner's attention to this matter.

Drawings

Applicants will submit formal drawings when there is an indication of allowable subject matter.

Specification

Applicants have amended the abstract as described above and submit that the amendment does not include new material. Applicants respectfully request the Examiner to withdraw this objection.

Applicants have amended the specification to correct the informalities that the Examiner noted in paragraph 16 of the Office Action.

Applicants have amended the specification such that the symbol for the unit "liter" is uniform.

Applicants have amended the specification to delete the term "micron" and replace it with the term - -micrometer- -. Also, Applicants have amended the specification to clarify the abbreviations "ppm" and "rpm". Also, Applicants have amended the specification to clarify the phrase % by weight".

Applicants have amended the specification such that the noted trademarks are capitalized and followed by the generic terminology.

Applicants submit that the amendments do not introduce new matter into the specification. Applicants respectfully request the Examiner to enter the amendments. Applicants respectfully request the Examiner to withdraw this objection.

Claims

Claim 30 is objected to for failing to further limit the subject matter of a previous claim. Applicants submit that the amendment of claim 28 serves to negate this objection. Applicants respectfully request the Examiner to withdraw this rejection.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 28-36 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because the "specification does not enable a method to *reduce* the signal-to-noise ratio".

Applicants have amended the claims such that they are directed to a method to increase the signal-to-noise ratio. As the Examiner noted on p. 7 line 2 of the Office Action, the specification is directed to a method for increasing the signal-to-noise ratio. Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

Rejection Under 35 U.S.C. §103

Claims 28-38 are rejected under 35 U.S.C. §103 as being unpatentable over Singer *et al.* (US 5,866,331). The Examiner's basic position is that in teaching a method of determining the total fluorescence intensity of a sample (probe), Singer renders obvious the invention

described in the present claims. Applicants respectfully traverse.

By way of review, the present invention is directed to an increase in the signal-to-noise ratio in a sensor array by summing individual sensor elements. That is, an array comprising a variety of subpopulations of different sensor elements is used. Each subpopulation comprises a plurality of identical sensor elements. Thus a level of redundancy is built into the array. By summing the responses of each sensor element in the subpopulation, the signal-to-noise ratio is increased.

In contrast, Singer is directed to methods for single molecule detection in *in situ* hybridization of an individual probe bound to a target molecule. This is done by binding a probe, with a defined number of fluorochromes, to a sample section. A digital imaging fluorescence microscope is used to digitally record a series of optical sections. The total fluorescence intensity (TFI) per fluorchrome is then determined, which can then be used to calculate the number of probes bound, which in turn is a determination of the presence of the target molecule.

The Examiner's points about Singer relate to the calculation of the TFI. In fact, the passages referenced by the Examiner are directed to the summing of individual pixels within the optical section and are explicitly in the context of determining the TFI of a single molecule (see col. 6, line 55). That is, the optical section covers a plurality of pixels, and to get the sum TFI, these pixels are summed to give the total fluorescence, and then the total fluorescence is essentially divided by the volume of the optical section to give an average, of sorts. However, the individual pixels are all part of a single "spot", essentially; to use applicants' language, the individual pixels are all part of an individual "sensor element".

Applicants respectfully remind the Examiner that a valid rejection under 35 U.S.C. §103 based upon a single prior art reference must be supported by some suggestion of the claimed invention or motivation to reach the claimed invention which is found in that single prior art reference. In re Laskowski, 10 USPQ2d 1397 (CAFC 1989).

To this end Applicants submit that there is no teaching or suggestion in Singer to practice the claimed invention. First of all, Singer is directed to *in situ* hybridization techniques. That is, a cell or tissue sample is on a slide, and it is exposed to a single type of

probe with one or more fluorochromes. There is no suggestion of arrays of subpopulations of different sensor elements.

The Examiner points to column 7, lines 1-2 of Singer as evidence of the teaching of subpopulations; however, we respectfully disagree with this assertion. The teaching of Singer refers only to a probe solution; this does not teach or suggest subpopulations of sensor elements.

The Examiner asserts that "all pixels" represents at least two of the sensor elements of at least one of the subpopulations. We respectfully disagree on the ground that the "all pixels" recited in Singer are all imaging a single type of fluorochrome. In addition, a pixel is defined as "the smallest element of a digital image that can be assigned a gray level", or "that can be assigned independent characteristics" (see *The New IEEE Standard Dictionary of Electrical and Electronics Terms*, copyright 1993, enclosed as Exhibit B). Thus, summing of pixels as described in Singer merely represents summing the individual elements representing the image of the total fluorescence from a sample. These elements are not individual sensor elements, but rather are a result of the imaging process. Applicants submit that Singer neither teaches nor suggests that the pixels represent subpopulations of independent sensor elements.

Furthermore, the Examiner is respectfully directed to Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 230 USPQ 416 (Fed. Cir. 1986) where the Federal Circuit held that a single line in a prior art reference should not be taken out of context and relied upon to show obviousness under 35 U.S.C. § 103. Rather, the Federal Circuit held that a prior art reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered.

To this end Applicants respectfully remind the Examiner that the purpose for summing the pixels in the Singer reference is so that the sum can be divided by the total number of fluorochrome molecules in the imaged volume to determine the total fluorescence intensity of a single fluorochrome under a given set of imaging conditions. Thus, the teaching of Singer as a whole is to sum the fluorescence of a given area (that includes only signals from a single element) and divide that sum by the total number of fluorochromes determined to be in that

sample. The present invention, however, is directed to a method of increasing the signal-to-noise ratio of a sensor array by measuring the optical response of at least two of the sensor elements of at least one of the subpopulations and summing the optical response signatures. The advantage of the present invention over the Singer reference is that by summing the optical response signatures from at least two sensor elements, the sensitivity of the sensor is increased while the signal-to-noise ratio is increased (see p. 13, lines 7- 10 of the specification as filed).

The whole point of Singer is to detect single molecules in an *in situ* cell or tissue sample. Thus, for example, Singer wants to be able to see individual beta- and gamma-actin mRNA (see for example, the experiments at column 15, line 59 through column17, line 34). If the methods of the present invention were used in Singer, summing of the signal of several of these target molecules together would render the data ineffectual for Singer's purposes. As outlined in M.P.E.P. §2143.01,"[i]f the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

Accordingly, the applicants submit that a prima facie case of obviousness has not been made and that the claimed invention, taken as a whole at the time the invention was filed, would not have been obvious to one of skill in the art. Applicants respectfully request the Examiner to withdraw this rejection.

Conclusion

Applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Respectfully submitted,

for Robin M. Silva
Reg No. 38,304

Date: February 11, 2000

1004365

Pending claims:

28. (Amended) A method for [reducing] increasing the signal-to-noise ratio in the characteristic optical response signature of a sensor array having subpopulations of different sensor elements comprising:

a) measuring the optical response signature of at least two of said sensor elements of at least one of said subpopulations; and

b) summing the optical response signatures.

29. A method according to claim 28 wherein prior to said summing, the baseline of at least one optical response signature is adjusted.

30. A method according to claim 28 wherein the signal-to-noise ratio is increased by a factor of at least 10.

31. The method of claim 28 wherein an analyte detection limit is reduced by a factor of at least 100.

32. The method of claim 28 wherein said sensor array comprises a population of beads dispersed on a substrate.

33. The method of claim 32 wherein said substrate is a fiber optic bundle.

34. The method of claim 32 further comprising identifying the location of each sensor element within each sensor subpopulation within the array.

35. The method according to claim 28 wherein said sensor elements comprise chemical functional groups.

36. The method according to claim 28 wherein said sensor elements comprise oligonucleotides.

37. (Amended) A method for amplifying the characteristic optical response signature of a sensor array having subpopulations of <u>different</u> sensor elements comprising:

a) measuring the optical response signature of at least two of said sensor elements of at least one of said subpopulations; and

b) summing the optical response signatures.

38. A method according to claim 37 wherein prior to said summing, the baseline of at least one optical response signature is adjusted.